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COPD AND ARDS:

What's Important For You to Know?

- **Basic lung anatomy histology (airways vs. alveolar regions).**
- **PFT's ("obstructive" vs. "restrictive" abnormalities).**
- **Pay attention to: emphysema, chronic bronchitis, bronchiectasis, asthma.**
- **Clinical and radiologic differences between chronic bronchitis and emphysema (see table).**
- **Role of smoking and PiZZ genotype in emphysema.**
- **Concept of the acinus and its relationship to the types of emphysema.**
- **Pay attention to: clinical classification of different types of asthma.**
- **Pay attention to: clinical settings that predispose to ARDS.**
- **Pathology of ARDS (acute vs. proliferative phases).**

Case Study: A 47-year-old female army LTC had received a renal transplant 4 months previously and was immunosuppressed with cyclosporine and prednisone. Five days prior to hospital admission, she developed progressive dyspnea on exertion with a dry cough, shaking chills, and a fever (101° F). After 24 hours, her temperature rose to 103° F, and she became hypotensive (85/60 mm Hg) and tachypneic. Her condition deteriorated, with the development of severe hypoxemia (Pa_{O2} = 77 mm Hg; Pa_{CO2} = 31 mm Hg), respiratory alkalosis (pH = 7.47), and reduced pulmonary compliance (23 cc/cm H_2O).

Gross Structure of the Airways: The airways arise as a series of 23 generations of dichotomous branches. The first 16-17 generations of branchings (bronchi + larger and terminal bronchioles) are purely ***conducting airways***. Conducting airways < 2 mm in diameter are ***terminal bronchioles***. The terminal 6-7 branchings (respiratory bronchioles + alveolar ducts + alveolar sacs) comprise the ***acinus*** (or ***terminal respiratory unit***) → are involved in *gas exchange* (i.e., alveoli can arise directly from any of these small airways). A ***pulmonary lobule*** comprises ± 3-5 acini. The right main stem bronchus is more vertical than the left → aspirated foreign material (e.g., vomitus and foreign bodies) tends to enter the right lung > the left lung → can result in atelectasis and pneumonia.

Microscopic Structure of the Airways and Alveoli: The conducting airways are lined by ***pseudo-stratified, columnar, ciliated epithelium***. The bronchial (but not the bronchiolar) epithelium also has mucus-secreting ***goblet cells*** as well as ***neuroendocrine (Kulchitsky) cells*** that contain dense-core, neurosecretory granules (detectable on E.M.). The bronchi (but not the bronchioles) also contain ***cartilage***. The epithelium of the smallest bronchioles contains non-ciliated ***Clara cells***. Flattened ***type I pneumocytes*** line ± 95% of the alveolar surface and cuboidal ***type II pneumocytes*** cover ± 5% of the alveolar surface. Type II cells produce ***surfactant*** and have lamellar bodies on E.M. When the alveolar epithelium is injured (e.g., in ***adult respiratory***

distress syndrome), type II pneumocytes regenerate → give rise to type I pneumocytes. The alveolar spaces are separated by ***alveolar septa*** (comprising ***capillaries*** and ***interstitial cells***). The endothelium and alveolar epithelium are separated by a ***basement membrane***. ***Myofibroblasts*** within the alveolar septa produce extracelluar matrix constituents — are "key players" in the pathogenesis of ***interstitial pulmonary fibrosis***.

Obstructive vs.Rrestrictive Airway Disease: From a clinical standpoint, It is important to categorize patients' respiratory symptoms as being due to either *obstruction* or *restriction*, as this will influence treatment.

Obstructive Disease: This term implies ***increased resistance to airflow***. Pulmonary function tests show ***increased pulmonary resistance*** with ***decreased maximal expiratory flow rates*** during forced expiration. The ***FEV_1*** and ***FEV_1/FVC ratio*** are the most useful measurements for assessment of large airways obstruction. The FEV_1 is reduced more than the FVC, consequently the ***FEV_1/FVC ratio is low***. The ***residual volume*** (***RV***) and ***total lung capacity*** (***TLC***) also are ***increased in obstructive disease***. The ***maximum mid-expiratory flow rate*** (***$FEF_{25-75\%}$***) is useful for measuring ***small airways obstruction***.

Causes of Obstructive Pulmonary Disease:

- **Tumor** → intraluminal or extrinsic compression. Respiratory obstruction may be intrathoracic (e.g., *bronchogenic carcinoma*) or extrathoracic (e.g., thyromegaly).
- **Foreign body**.
- **Emphysema** → loss of supporting parenchyma allows collapse of airways.
- **Chronic bronchitis** → secretions and hyperplasia obstruct airways.
- **Bronchial asthma** → reversible airways obstruction.
- **Bronchiectasis** → airways become dilated and floppy.

Restrictive Disease: Characterized by reduced expansion of lung parenchyma with decreased **total lung capacity (TLC)** and normal flow rates. The **FEV1/FVC ratio** is unchanged. **Affected patients may also have a decreased diffusing capacity (DL_{CO}) if restriction is due to interstitial lung disease**. (A review of pulmonary function tests for clinicians by R.O. Crapo can be found in the *N. Engl. J. Med.* 331:25-30, 1994).

Causes of Restrictive Disease:

- **Chest wall diseases with normal lungs** (e.g., ***neuromuscular diseases*** like polio or muscular dystrophy, marked ***obesity***, or ***kyphoscoliosis***).
- **Interstitial or infiltrative pulmonary parenchymal diseases** (e.g., ***idiopathic fibrosis*** or the ***pneumoconioses***).

Arterial Blood Gases (ABG): These are used to assess oxygenation and acid-base balance. *ABG must be collected properly, labeled correctly, and run immediately, or else they are useless!* (*Acid-base balance* is beyond the scope of this lecture topic. "A practical approach to acid-base disorders" by R.J. Haber has some good tips and can

be found in *West. J. Med.* 155:146-151, 1991. **This is FYI only** and is not required reading).

Chronic Obstructive Pulmonary Disease (COPD): COPD includes a group of diseases that are characterized by chronic or recurrent obstruction of airflow within the lung to a degree that produces *functional disability*. The obstruction to airflow is produced by a number of different anatomic abnormalities including ***increased luminal secretions*** (due to smoking or cystic fibrosis), ***thickening of the airway wall*** (due to edema or hypertrophy), or ***loss of the elastic recoil of the airway*** (due to parenchymal destruction). **There are 4 main categories of COPD — emphysema, chronic bronchitis, bronchiectasis, and asthma**.

Emphysema: This is a disease of the lung characterized by abnormal, permanent enlargement of the acini (i.e., air spaces distal to the terminal bronchiole) due to destruction of their walls.

Prevalence of Emphysema. Emphysema is an extremely common disease in this country. The incidence increases with age and it is more common in men than women. It is strongly associated with cigarette smoking.

Types of emphysema:

- **Centriacinar (centrilobular)**. Characterized by dilatation predominantly involving the central or proximal acinus (or the respiratory bronchiole) while sparing the distal alveoli. It tends to be more severe in the upper lobes, is most frequent in male smokers, and often coexists with ***chronic bronchitis***.
- **Panacinar (panlobular)**. Characterized by uniform dilatation of the entire acinus. It is more common in the lower lobes and is associated with ***α_1-antitrypsin deficiency***.
- **Paraseptal (distal acinar)**. This type is most obvious adjacent to the pleura, often near areas of scarring. It tends to involve the distal acinus predominantly and may be associated with ***spontaneous*** **pneumothorax** in young adults.
- **Irregular**. There is irregular involvement of the acinus associated with scarring.

Pathology of Emphysema: The diagnosis and classification of emphysema is primarily based on gross examination of inflated lung specimens. As the disease becomes more severe, often it is not possible to accurately classify the type of emphysema!

Pathogenesis of Emphysema: There is a strong correlation between emphysema and heavy cigarette smoking. Emphysema also complicates certain types of **coal workers' pneumoconiosis**. The most plausible current hypothesis for the destruction of alveolar walls that occurs in emphysema is the so-called **protease-antiprotease theory** — ***destruction results from an imbalance between proteases (elastase) and***

antiproteases. Conditions which increase protease secretion or decrease antiproteases function favor destruction of elastic tissue. Elastases are released predominantly from neutrophils, with possible contributions from macrophages, mast cells, and bacteria. Also, cigarette smoke is chemotactic for neutrophils and stimulates the release of neutrophil elastase. At the same time, oxidants released from neutrophils and which are present in tobacco smoke inhibit the action of α_1-antitrypsin.

α_1-antitrypsin deficiency: The protein, α_1-antitrypsin, is encoded by a set of allelic genes on the ***proteinase inhibitor (Pi) locus*** on chromosome 14. Of at least 75 different allelic variants, the normal genotype, ***PiMM***, is present in $\pm$ 90% of the population. Individuals with the homozygous ***PiZZ genotype***, which occurs in $\pm$ 0.01% of the U.S. population, develop severe, ***early-onset emphysema*** which is greatly increased in severity by cigarette smoking.

Clinical Consequences of Emphysema: The classic clinical presentation of a patient with emphysema is that of a ***"pink puffer"*** who develops progressive dyspnea in association with a barrel-chest and slowing of forced expiration (i.e., a reduced FEV_1). Although their ABG are normal, patients have a reduced DL_{CO}. Patients may be unaware of deterioration in lung function until they reach a critical point. Complications include ***massive pneumothorax***, ***cor pulmonale***, ***respiratory acidosis*** and ***coma***.

Chronic Bronchitis: The definition of chronic bronchitis is a clinical one. *Chronic bronchitis is present if a patient has had a persistent cough with sputum production for at least 3 months in at least 2 consecutive years*.

Prevalence of Chronic Bronchitis: This disease is most common among smokers but also afflicts residents of polluted urban areas. It occurs most frequently among middle-aged men.

Pathogenesis of Chronic Bronchitis: A number of factors play a role in the development of chronic bronchitis:

- **Chronic irritation by inhaled substances** (e.g., **cigarette smoking** and **pollutants**).
- **Repeated pulmonary infections** → recruitment of neutrophils that release proteases.

Pathology of Chronic Bronchitis: The following features are observed:

- **Hypertrophy of submucosal glands** in the trachea and bronchial walls. The so-called *Reid index* is a measure of the ratio of the thickness of the mucous gland layer to the wall (normally, it should be < 0.5 whereas it is increased in chronic bronchitis).
- **Hyperplasia of goblet cells** in the small airways
- **Hypersecretion of mucus** → leads to **obstructive airways disease**.

Clinical Consequences of Chronic Bronchitis: In the early stages, patients have a

persistent cough productive of abundant sputum. Later, symptoms of **COPD** develop (i.e., ***hypercapnia***, ***hypoxemia***, ***mild cyanosis***, and, eventually, ***exertional dyspnea***, ***cor pulmonale***, and ***congestive cardiac failure***). Chronic smokers frequently develop smoking-related **atypical metaplasia** and **dysplasia of the bronchial epithelium**.

DIFFERENCES BETWEEN CHRONIC BRONCHITIS AND EMPHYSEMA

CLINICAL FEATURE	CHRONIC BRONCHITIS	EMPHYSEMA
Appearance	"Blue bloater"	"Pink puffer"
Usual age group	40-45 years	50-75 years
Cough	Early cough ⇒ sputum +++	Late cough ⇒ sputum ±
Infections	Common	Occasional
Respiratory failure or insufficiency	Repeated	Terminal
Cor pulmonale	Common	Rare, terminal event
Airways resistance	Increased +++	Normal or increased ±
Elastic recoil	Normal	Low
Appearances of chest radiographs	Prominent vessels with an enlarged heart	Hyperinflation with a small heart

Bronchiectasis: This represents a chronic necrotizing infection of the bronchi and bronchioles associated with abnormal, irreversible dilatation of the airways and excessive sputum production.

Etiology of Bronchiectasis: With the availability of antibiotics, bronchiectasis is less common now than previously. **Causes:**

- **Bronchial obstruction** — either intrinsic or extrinsic.
- **Necrotizing pneumonia**.
- **Congenital or hereditary diseases**:
  - **Cystic fibrosis** is an autosomal recessive disorder due to a single mutation on the long arm of chromosome 7 ⟶ encodes an abnormal chloride channel protein, the ***cystic fibrosis transmembrane conductance regulator***. There is a basic defect in chloride transport associated with thick, viscid secretions in the gastrointestinal, respiratory, hepatobiliary, and male genital tracts. Patients are especially prone to ***Pseudomonas aeruginosa*** pulmonary infections.
  - **Kartagener's syndrome** is associated with abnormalities in ciliary architecture and function and is characterized by a lack of ciliary motility due to absent or ***abnormal dynein arms*** ⇒ infections of sinuses and bronchi and impaired cell motility during embryogenesis. It comprises a triad of ***sinusitis***, ***situs inversus***

and ***bronchiectasis***. Impaired motility of spermatozoa → male sterility.

■ **Intralobar sequestration** → lung lobes lack a normal connection to the airway system → bronchial distension due to accumulation of secretions.

Pathology of Bronchiectasis: Manifestations of ***infection*** and ***obstruction*** associated with abnormal dilatation of the bronchi and bronchioles are observed. Grossly, the bronchi may show **cylindroid**, **saccular**, or **fusiform dilatations**. Microscopically, the airway epithelium may show **ulceration** and/or **metaplasia**. Some bronchiolar lumina may be occluded by granulation tissue -- **bronchiolitis obliterans**.

Asthma: Asthma is a manifestation of *reactive airways disease* characterized by ***hyperresponsiveness of the tracheobronchial tree***, leading to paroxysmal narrowing of the airways (i.e., ***bronchospasm***). ± 10% of children and ± 5% of adults have asthma.

Pathogenesis of Asthma: All types of asthma have a characteristic hyperreactivity of the airways to irritants and bronchoconstrictor agents. Airway hyperreactivity results from the ***release of inflammatory mediators*** (e.g., histamine, leukotriene B_4, leukotrienes C_4, D_4, and E_4, prostaglandin D_2, platelet activating factor, IL-2, IL-3, IL-4, IL-5, and GM-CSF).

Pathology of Asthma: It is rare for the pathologist to have an opportunity to observe the histologic features of asthma. When present, they are detected at autopsy in patients with severe **status asthmaticus** (intractable asthma). ***Histology*:**

- **Hypertrophy of bronchial smooth muscle**.
- **Thickening of the basement membrane** of the bronchial epithelium.
- **Bronchial Inflammatory infiltrate** showing prominent ***eosinophilia***.
- **Hyperplasia of the submucosal mucous glands** ⇒ increased ***Reid index***.
- Occlusion of bronchi and bronchioles by thick mucus plugs containing ***Curschmann's spirals*** (long whorls of mucus and shed epithelium), ***Charcot-Leyden crystals*** (crystals of eosinophilic debris), and ***Creola bodies*** (sloughed fragments of mucosa).

Classification of Asthma: Clinically, asthma can be classified according to the nature of the stimulus which provokes the hyperirritability of the airways. Some patients have only one trigger (e.g., exercise) while others react to a variety of stimuli. Traditionally, asthma has been divided into *extrinsic* (allergic) and *intrinsic* (non-allergic) varieties. However, many people with extrinsic asthma also will react to cold, irritants or other non-immunologic provocations. **The main clinical types of asthma are:**

- **Atopic (or extrinsic) asthma**. This is the most common type of asthma and represents an example of an ***IgE-mediated, type I hypersensitivity reaction***. This usually is seen in childhood and is triggered by ***inhaled allergens*** (e.g., ragweed, grass pollens, house dust, and animal dander).

- **Intrinsic (or late-onset) asthma** – typically first manifests in adults > 30 years old. It is triggered by irritants, cold, anxiety, and respiratory tract infections (e.g., ***rhinoviruses*** and ***parainfluenza viruses***). Some cases appear to relate to hyperirritability of the parasympathetic system or to β-adrenergic receptor blockade.
- **Exercise-induced bronchospasm** – seen especially with jogging.
- **Aspirin-sensitive asthma** – association of ***nasal polyps***, *sinusitis,* and *asthma* with sensitivity to acetyl salicylate and other cyclooxygenase inhibitors.
- **Occupational asthma** – triggered by chemical dusts, fumes, and gases.
- **Allergic bronchopulmonary aspergillosis** – triggered by contact with spores of the fungus, ***Aspergillus fumigatus***.

Factors Exacerbating Any Type of Asthma: These include ***sinusitis***, ***acute infection***, and ***gastro-esophageal reflux***. Rarely, recurrent showers of pulmonary emboli may present with or exacerbate asthma.

Clinical Consequences of Asthma: These include the following:

- **Wheezing** is the most characteristic symptom → prolonged expiration.
- Attacks may last for several hours-to-days.
- Prolonged coughing up of **tenacious secretions** when attacks cease.

Treatment of Asthma:

- **Inhaled bronchodilators** (β_2-agonists).
- **Inhaled steroids**.
- **Leukotriene antagonists**.
- **Theophylline**.
- Attacks in children can be **prevented** by the use of **sodium cromoglycate**.

Complications of Asthma:

- **Pneumothorax** and **pneumomediastinum**.
- **Status asthmaticus**.
- Superimposed infections may result in **bronchitis**, **bronchiectasis**, or **pneumonia**.
- **Death** – asthma mortality rates have been increasing recently, especially in children. Indicators of a potentially bad outcome include steroid dependence, frequent emergency room visits, and a history of severe attacks that require hospitalization.

Adult Respiratory Distress Syndrome (ARDS): This represents a clinical syndrome characterized by decreasing compliance, widening of the alveolar-arterial (A-a) oxygen gradient, and the appearance of chest X-ray infiltrates following acute lung injury caused by a wide variety of agents. The histopathologic changes seen in ARDS are referred to as ***diffuse alveolar damage*** (***DAD***).

Etiology of ARDS: This syndrome usually develops in patients previously hospitalized for some underlying ***clinical catastrophe***:

- **Shock** associated with ***trauma***, ***burns***, ***abdominal surgery***, or ***sepsis***.
- **Pulmonary infections** (viral, bacterial or fungal).
- **Inhalational injury** (e.g., ***oxygen toxicity***, ***smoke inhalation***, or ***NO_2 exposure***).
- **Drugs** (e.g., ***chemotherapy***, ***heroin***, or ***paraquat***).
- **Aspiration** (e.g., of ***gastric contents*** or due to ***drowning***).
- **Systemic diseases** (e.g., ***pancreatitis*** or ***uremia***).
- **Cardiac surgery** with **cardio-pulmonary by-pass**.
- **Miscellaneous** (e.g., trips to ***high altitude*** or ***amniotic fluid embolism***).

Pathogenesis of ARDS: The initial stimulus causes injury to both alveolar septal endothelial cells and alveolar epithelial cells → exudation of protein-rich fluid into the alveolar space → exudate comprises fibrin strands and necrotic cellular debris → formation of *hyaline membranes* that line the alveolar walls. **Mechanisms:**

- **Complement activation** → intravascular aggregation of neutrophils → release of oxygen-derived free radicals ($\bullet O_2^-$ and •OH), reactive nitrogen species (peroxynitrite anion: $ONOO^-$), lysosomal enzymes, and products of arachidonic acid metabolism → injury to endothelial cells and type I pneumocytes.
- **Sepsis** → endotoxin release → alveolar macrophage activation → release of cytokines (TNF-α and IL-8), oxygen-derived free radicals, reactive nitrogen species, and arachidonic acid metabolites.
  - ■ **IL-8** → chemoattractant for neutrophils.
  - ■ **TNF-α** → activation of ***adhesion molecules*** (e.g., ICAM-1) on endothelial cells → enhanced attachment of neutrophils to endothelium.

Pathology of ARDS:

- Gross findings – the lungs are heavy, solid, and appear dark red.
- **The microscopic features of DAD will vary** depending on the time of the initial insult, the onset of symptoms, and the timing of the biopsy. **Stages:**

■ **Acute or exudative stage** – interstitial or intra-alveolar edema, hyaline membranes, interstitial inflammation, and fibrin thrombi within alveolar capillaries and small pulmonary arteries.

■ **Proliferative or organizing stage** – ***type II pneumocyte hyperplasia*** and ***atypia***, with ***intra-alveolar and alveolar septal fibrosis*** → progressing to dense fibrosis.

Clinical Features of ARDS:

- Acute onset (or worsening) of **dyspnea**.
- **Diffuse pulmonary infiltrates** on chest X-ray (so-called ***"non-cardiogenic pulmonary edema"***).
- **Tachypnea**, **cyanosis**, and **refractory hypoxemia** are seen.
- **High inflation pressure requirements** during ventilation.

Incidence and Outcome of ARDS: Of patients at risk (with predisposing conditions such as burns or shock), + 7-11% will develop ARDS. If more than one risk factor is present, + 25% will develop ARDS. **The overall mortality rate for ARDS is + 50-90%**.